Research and Global Health Emergencies

Research and Global Health Emergencies: On the Essential Role of Best Practice

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This article addresses an important, overlooked regulatory challenge during global health emergencies (GHEs). It provides novel insights into how, and why, best practice can support decision makers in interpreting and implementing key guidance on conducting research during GHEs. The ability to conduct research before, during and after such events is crucial. The recent West-African Ebola outbreaks and the Zika virus have highlighted considerable room for improvement in meeting the imperative to research and rapidly develop effective therapies. A means of effectively capturing these experiences and folding them into future decision-making is lacking; the need for effective practical translational measures remains. The challenge for the research community lies in extracting meaningful action-guiding content from pre-existing guidelines—which draw upon practical examples of guidelines 'in action'—that assist in determining how to act in a particular (future) situation. Insights are provided into the role of best practice as a means to do so; such examples can provide invaluable support to decision makers in interpreting high-level guidance; overarching guidelines retain their necessary level of generality and flexibility, whilst corresponding best practice examples—which incorporate important lessons learned—illustrate how such guidelines can be interpreted at a practical level.

Introduction

Global health emergencies (GHEs) trigger profound immediate and long-lasting consequences at the local, national and international levels, as evidenced by H5N1, the more recent West-African Ebola Outbreak and the ongoing Zika virus crisis. The World Health Organization (WHO) is responsible for declaring when such an emergency arises (what it officially refers to as a 'Public Health Emergency of International Concern' or 'PHEIC'). Under the International Health Regulations (IHR) 2005, a PHEIC is defined as 'an extraordinary event which is determined: a. to constitute a public health risk to other States through the international spread of disease; and b. to potentially require a coordinated international response' (WHO, 2015b).[1]

GHEs engage a broad spectrum of actors and institutions. Individual states are responsible for notifying the WHO of potential GHEs, for surveilling and containing the spread of disease, as well as offering treatment to their citizens. Given that GHEs 'do not respect national borders' (WHO, 2016), governments are also obliged to take into consideration the needs of other countries (particularly those of low-income countries). At the international level, the WHO is responsible for coordinating international response. However, numerous additional actors play key roles in managing responses to GHEs,[2] including researchers and research institutions; governments; nongovernmental organizations (NGOs); pharmaceutical companies; international organizations; and collaborative networks (Ganguli Mitra and Sethi, 2016). Indeed, each GHE has the tendency to catalyse the establishment of more (increasingly international) global health collaborations, particularly in the form of public private partnerships.

The ability to conduct research is particularly important in the GHE setting, in cases where novel pathogenic viruses emerge and corresponding therapeutics are nonexistent (as demonstrated with Ebola and Zika), as well as to track the spread of already identified viruses. While 'the need to learn as much as possible as quickly as possible' (WHO, 2016: 30) has been stressed, most recently in the revised Council for International Organization for Medical Sciences (CIOMS) guidelines, the relationship between response and research gives rise to numerous (ethical and regulatory) tensions. For example, despite the distinct regulatory mechanisms for offering treatment versus conducting research (Calain *et al.*, 2009: 10), the lines between the two activities are

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easily blurred (Kass *et al.*, 2013; Willison *et al.*, 2014) particularly during GHEs (Hunt *et al.*, 2012). Further complexity is added given that the research community is subject to various—at times conflicting—obligations, which stem from a variety of sources. Interactions between national and international laws are often complicated, and the ambiguous obligations derived out of various codes and treaties give rise to further uncertainties around the application of guidelines (Irwin, 2010; Gostin *et al.*, 2015).

Given these complexities, this article deals with two related but distinct and equally pressing issues. First, despite the numerous guidelines engaged when research takes place during GHEs, the interpretation of pre-existing guidelines is challenging and decision makers require additional support in applying guidelines concretely. Further, it has been noted that despite the emerging guidance on 'lessons learned' from GHEs (most recently from Ebola and Zika), what is lacking—and needed—is increased effort to 'translate' these lessons into policy and practice (Smith and Upshur, 2015). Whilst reports have highlighted the need for greater investment in prevention, domestically and internationally (WHO, 2015a) the ways in which both (i) interpretation of guidance can be supported and (ii) lessons learned can be incorporated into pre-existing guidance, have not received the attention that they demand. Given the numerous and profound effects which GHEs can have on individuals, and the integral role of research in mitigating these effects, it is imperative that we support the research community in navigating the challenging issues which arise in the GHE context.

In tending to this problem, this article advances an approach that can support decision makers in interpreting and extracting meaningful action-guiding content from guidelines in a manner which captures practical realities and lessons learned from previous GHE experiences. It is argued here that the introduction of best practice examples alongside pre-exiting guidance can provide this assistance. The discussion draws heavily on the problems highlighted during recent GHEs, and considers how best practice can serve to implement some of the solutions which have been advanced to ensure better preparedness for future health emergencies, a core aspect of which relies upon research activities.

First, the importance of current dominant approaches to decision-making in the form of 'principle-like' and 'rule-like' guidelines is considered. An important first-step in appreciating the value of best practice lies in appreciating the challenges associated with rules and principles. It becomes apparent that these leave the decision maker wanting more in terms of determining 'what to do'. Next, a novel perspective is offered on the role of best practice instantiations as a more effective alternative, complementary to existing analyses. The best practice approach represents a middle ground between principle-like and rule-like guidelines and offers valuable interpretative support to decision makers whilst simultaneously capturing and reflecting lessons learned from previous GHEs. This assists the translation of the abstract *text* to the concrete *context* in a robust and ethically defensible manner.

Current Challenges in Interpreting Guidance

This section considers some core challenges of interpreting guidance on conducting research during GHEs. Whilst discussion on the strengths and limitations of principle or rule-based decision-making has taken place at a general level,[3] it has focussed on the substance of principles or rules rather than their suitability as decision-making tools *per se*. For example, in the GHE and research context, contributions analyse the suitability of different values and norms reflected within guidance and regulatory frameworks, e.g. social value in research (Ganguli-Mitra *et al.*, 2017), protection of vulnerable populations (MacIntyre and Travaglia, 2015) or the repercussions of procedural requirements stipulated within guidance (e.g. exclusion of pregnant women from vaccine trials as considered by the Ethics Working Group on ZIKV Research and Pregnancy, 2017). Similarly, discussions on international obligations focus on (lack of) enforceability of guidance, given their often aspirational nature or status as 'soft norms' (Gostin *et al.*, 2015) or their content, as opposed to the suitability of such guidance in supporting decision makers in their interpretation of guidelines.

In moving beyond these existing discussions, first, I consider the strengths and weaknesses of pre-existing approaches, i.e. principle-like guidance and rule-like guidance. The key theme that emerges is that while numerous guidelines on GHEs exist, understanding how to implement these in practice can be problematic. What is lacking is a middle-ground approach which, as I argue in the subsequent section, can be provided by the inclusion of best practice examples within decision-making models.

Principle-like and Rule-like Approaches

Current instruction on conducting research during GHEs often takes the form of principle-like or rule-like guidance. Principle-like guidance typically manifests as broad, abstract and high-level norms. In contrast, rule-like guidance tends to be more specific and prescriptive. Legal philosophy differentiates between the two as follows: principles are optimization requirements, which can be satisfied to varying degrees (Alexy, 2002), whereas rules are applicable 'in an all or nothing fashion' (they either apply to a given scenario or do not) (Dworkin, 1967). Within bioethics, discussions have tended to focus on ethical principles and their suitability in resolving dilemmas. Criticisms of principle-based approaches centre on the difficulty in extracting meaningful action-guiding content from vague abstract norms (e.g. Clouser and Gert, 1990: Martin and Singer, 2003; Muirhead, 2012; Grill and Dawson, 2017) and how to reconcile conflicting principles via balancing (Grill and Dawson, 2017). Within regulatory theory, there has been a recent proliferation of discussion on principle-based regulation and rule-based regulation (e.g. Black, 2010, Devaney, 2011; Sethi, 2015): '. . .the former relies upon broad and looser principles to guide action and the latter upon stricter pre- and proscriptive rules for framing approaches to governance and decision-making' (Laurie and Sethi, 2013: 44).

For the purposes of this discussion, it would be tempting to caricature guidelines such as the Declaration of Helsinki as 'principles', and, in contradistinction, the International Health Regulations, and legislation more generally, as 'rules'. However, it is often difficult to tell whether we are in fact dealing with a principle or a rule (Laurie and Sethi, 2013). Consider for example, the guidelines contained in the CIOMS *International Ethical Guidelines for Health-related Research Involving Humans*, collectively referred to as 'rules and principles' (2016: xii); even a brief glance at the content included within them reveals that it is not always clear which are which.

Thus, this article resists the temptation to make categorical claims about whether particular guidance constitutes a principle or rule (or indeed, a 'norm' or 'value'). Rather, the focus is on how we can extract meaningful action-guiding content from current guidelines provided on conducting research during GHEs. This being said, to understand the limitations of vague and abstract guidance, as well as specific and prescriptive guidance, a shorthand means of referring to different forms of guidance is required. And so, for the purposes of this discussion, and in keeping with the definitions offered earlier, I refer to 'principle-like' and 'rule-like' guidelines throughout and do so thusly: (i) rule-like guidelines are considered to include norms which are typically specific and prescriptive, either applicable or not; whereas (ii) principle-like guidelines are considered as more abstract optimization maxims, applicable to varying degrees and which carry a dimension of weight, suggesting that different principles can be engaged in any given scenario, and conflict may arise between them. Such conceptualizations will be subject to criticism, but these heuristics nonetheless help to facilitate the discussion, which seeks to offer a practical solution to the research community during GHEs. To understand why current guidelines require additional interpretative support, the strengths and limitations of principle-like and rule-like approaches are considered next.

'Principle-like' Guidelines

The health research context hosts a variety of principle-like guidelines. Consider for example those contained within the Belmont Principles (e.g. 'respect for persons') and the Nuremberg Code (e.g. Principle 7: 'Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death'). Principle-like guidelines can serve various functions for decision makers (Sethi, 2015), two of which are particularly noteworthy here. First, they can provide a common framework and point of reference to support decision makers in engaging in dialogue with others, not only in terms of justifying decisions but also in communicating with stakeholders. For example, in the GHE context, researchers can appeal to principles to justify taking certain courses of action. Likewise, where articulated in an open and accessible manner, they can be used as a frame of reference to engage with research participants, the local community (the importance of which has been stressed in the new CIOMS guidelines, 2016, Guideline 7) and the (wider) research community including pharmaceutical companies and funding organizations around key ethical considerations.

However, the utility of such guidelines is limited when we turn to consider the second function which is based on a core claim that they provide a guiding function in assisting decision makers in determining what to do. Paradoxically, principle-like guidelines are problematized (e.g. Gert, Culver and Clouser, 2000) precisely because of the *lack* of (sufficient) action-guiding content. Even where such guidance is considerably more detailed than a mere nod to an ethical principle, e.g. 'respect for autonomy', it is still difficult to understand how to interpret

and apply the norm in a particular setting or context. For example, the Declaration of Helsinki states, 'Groups that are underrepresented in medical research should be provided appropriate access to participation in research'; while this guideline reminds us to provide access to underrepresented groups, it does not suggest what 'appropriate access' entails. Indeed, a key challenge of principle-like guidance speaks to the vague and abstract nature of principles (Clouser and Gert, 1990), leaving too much room for interpretation and rendering it difficult for the decision maker to extract meaningful action-guiding content from such high-level norms (Clouser and Gert, 1990; Muirhead 2012). For example, The Draft Statement and Guidelines for Disaster Research states that '[a]ll research should be subject to local ethics review that includes regular feedback from the researchers and community representatives' (Sumathipala *et al.*, 2011). Eckenwiler *et al.* (2015: 656) lament the lack of guidance on what 'regular feedback' entails as a concept or process, and a lack of explanation of 'how researchers should identify and engage with community representatives on ethical concerns'. It appears that this interpretative challenge is widespread. For example, in their systematic review of guidelines for conducting research in disaster settings, Mezinska *et al.* (2016) have noted inconsistent use and application of key concepts such as 'risk management' and 'direct/indirect benefit'.

A particular complexity in the GHE context lies in the fact that deliberations around what to do necessitate room for context-specific considerations,[4] which can be a challenge when dealing with high-level guidelines. Although there may be overlapping ethical and legal considerations across different GHEs, each has the potential to bring to the fore unique and novel issues that are specific to the case in hand. For example, while both Ebola and Zika raised questions around containment, the latter attracted particular concerns around adverse pregnancy outcomes resulting from infection, raising specific questions around the inclusion of pregnant women in vaccine development. In commenting on the historical exclusion of pregnant woman from 'interventional biomedical research', the Ethics Working Group on ZIKV Research and Pregnancy suggests that investigators have been 'reticent' to conduct research on pregnant women partly due to 'misinterpretations or overly cautious interpretations of what is allowed under research regulations and international norms' (2017: 1). This serves as yet another example of the need to offer the research community additional support in the interpretation of guidelines.

Spatial and temporal considerations must also be factored-in; as Eckenwiler *et al.*, note (2015), the necessity for rapid response is heightened in the emergency setting, decisions must be taken quickly and obtaining robust and timely ethics review to carry out research can represent a significant challenge. Eckenwiler *et al.* have also pointed out the failure of the *Ethical Framework for the Development and Review of Health Research Proposals Involving Humanitarian Contexts* guideline on REC oversight. The authors state that in focussing on 'adverse events from vaccines, drugs, and medical procedures', the framework fails to include 'the range of emergent and evolving social, political and economic vulnerabilities to which researchers and RECs should ideally respond' (2015: 656). Context-specific guidance is also needed on the appropriate standard of care provided by researchers to research participants, which Mezinska *et al.* (2016) suggest is lacking amongst the guidelines on research which they have reviewed. Similarly, geographical challenges and limited access to willing and suitably informed research participants can be problematic (Levine *et al.*, 2004). Additionally, the potential of new technologies, particularly those around data sharing and analysis, have motivated the inclusion of new guidelines (e.g. CIOMS, 2016) the practical application of which necessitates further support for decision makers.

A further challenge that arises in principle-like guidelines is that given their dimension of weight, and the fact that more than one principle can be engaged in any given scenario, conflict can arise between principles. Balancing is often invoked as a means to resolve this conflict whereby each relevant principle is assigned a weight (e.g. Beauchamp and Childress, 2013). For example, in the case of Ebola, the imperative of rapid response had to be weighed against the principle of obtaining informed consent for the use of specimens for future research (Schopper *et al.*, 2017). However, balancing has been extensively problematized, given the lack of clarity on how to balance,[5] and the task of assigning weights to different principles has been described as 'measuring the immeasurable' (Frantz, 1963: 729). The WHO *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* (2016: 21) acknowledges the need to balance competing principles; for example, it considers the conflict which can arise between utility (maximizing benefit and minimizing burden) and equity (which relies on fair distribution). The Guidance recognizes recognizes that 'there is no single correct way to resolve potential tensions' between the principles and although the text highlights further considerations related to these principles (e.g. ensuring transparency in decision-making, the needs of vulnerable populations, reciprocity), it stops short of offering

concrete examples of *how* these principles can be justifiably balanced against each other.

'Rule-like' Guidelines

One solution towards addressing the challenge of knowing how to implement broad and abstract guidelines is to offer more prescriptive iterations of what to do (often in the form of rule-like guidelines), but these can easily become overly specific (Bennett Moses, 2007) and thus lose their necessary flexibility and applicability to a variety of different scenarios. Indeed, guidelines must cover a wide range of research activities 'from epidemiological and socio-behavioral to clinical trials and toxicity studies, all of which are crucial' (Kieny, 2016).

A prime example of overly specific guidance and the interpretative challenges, which it can give rise to, is evident from the avian influenza (H5N1) pandemic. Although wider debates around benefit-sharing and access to treatments dominated (Fidler, 2010; Smith, 2012), the pandemic raised important interpretative challenges to international regulations. Issues arose around the ownership of biological samples of viruses and delineating which obligations were incumbent upon states in terms of sharing these samples with other countries (Sedyaningsih *et al.*, 2008; Mullis 2009). Access to virus samples is paramount to identify pathogens and to develop appropriate treatments, particularly vaccines. Numerous varying interpretations around which obligations states must fulfil were discussed in the case of H5N1, and one argument advanced by Indonesia was that even though the then relevant International Health Regulations (1969) did oblige the sharing of biological virus samples between states, influenza was not *expressly* included as one of the diseases which was subject to those regulations (Fidler, 2008). Subsequent discussions made clear that the intention of the IHR was to include the sharing of influenza viruses. However, Indonesia attempted to rely upon an omission to explicitly include influenza within the relevant set of rules, thus rendering the lack of specificity open to varying interpretation. This led to a significant hold up for the research community in terms of gaining timely access to virus samples and developing vaccines in a setting where rapid response was crucial. More recently, it has been noted that prior to the Ebola outbreak, the majority of WHO ethics guidance was disease specific (e.g. focussing on ethical issues relating to tuberculosis). Ebola has highlighted the need for more general guidance for 'ethics in outbreaks and epidemics more generally' (Selgelid, 2016).

A further difficulty in the GHE research context is that pre-existing rule-like guidance—particularly legislation—can be both over- and under-inclusive of new technologies (Bennett Moses, 2007) which have the potential to transform and greatly improve the management of prevention/response/support activities for populations in crisis.[6] Consider the rapid technological developments which have taken place around the use of data, not only in terms of surveillance of GHE spread but for research purposes. One of the core drivers for the revision of the International Health Regulations (1969, as amended) was the need to establish a global surveillance system for GHEs (Baker and Fidler, 2006). In turn, the pre-existing IHR did not adequately reflect the need and related potential of data sharing to greatly strengthen both surveillance and research. While the revised IHR 2005 did strengthen requirements for surveillance, legal barriers remain an impediment against data sharing in the context of GHEs, not only during but after an emergency has taken place. For example Sane and Edelstein (2015: 10) report '. . .lack of formal or informal data-sharing agreements across borders, lack of an enforcement mechanism for the IHR, and intellectual property rights and data ownership, all hindered transparent sharing. Compliance with different national legislations was seen as particularly challenging'.

Another problem of overly prescriptive guidance is that such approaches can inhibit the research community from trying out new research methods which may actually constitute best practices in the particular context of a specific disease. Disputes arose around the most appropriate trial design for developing Ebola vaccines, with certain stakeholders insisting that methods should follow established protocols on randomized control trials, whilst others argued that flexibility to try alternative trial design was necessary (Caplan *et al.*, 2015; Keusch *et al.*, 2017). These disputes led to untimely delays in discovering 'safe and effective products in time to fight the epidemic'.[7] It is imperative that to avoid similar delays should a new GHE epidemic emerge—which raises similar questions around trial design—additional support is available to decision makers which folds in the experiences already.

Accompanying Text

It is important to acknowledge that, perhaps in recognition of the challenges and limitations of current guidelines, and of vague and abstract principle-like guidelines in particular, guidance on conducting research during GHEs is often accompanied by explanatory text. For example, each CIOMS guideline is supported by a

'commentary'. The WHO *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* (produced as a response to ethical issues raised by the Ebola outbreak) contains 14 specific guidelines, each of which is 'introduced by a series of questions that illustrate the scope of the ethical issues, followed by a more detailed discussion that articulates the rights and obligations of relevant stakeholders' (WHO, 2016: 10). Likewise, the 'Belmont Principles' are situated within a Part 3 Belmont Report (1979), which includes a statement on the distinction between treatment and research and 'remarks' about the application of the principles. Despite these valuable accompanying texts, I argue that we must go one step further in supporting decision makers in their interpretation of guidelines. The utility of explanatory text is limited because it often lacks concrete illustrations of how principles are worked through *in practice*, which reflect real-world examples and lessons learned from previous GHEs—a function which best practice examples perform.

Best Practice: Learning from the Ground up?

Thus far, we have considered the challenges which guidelines on conducting GHEs can present for those wishing to conduct research during this time. Both high-level and prescriptive guidelines have their own strengths and drawbacks, interpretative challenges remain and a means of capturing 'lessons learned' effectively is often lacking. A mid-level approach is needed which simultaneously (i) retains the flexibility of principle-like guidelines and avoids the pitfalls of overly specific rule-like guidelines; (ii) supports decision makers in extracting action-guiding content from guidelines and (iii) folds in important lessons already acquired from previous GHEs. The remaining sections consider in turn how the inclusion of best practice examples in guidance can meet all of these requirements.

Best Practice: Making the Most out of Principle-like and Rule-like Guidelines

As considered earlier, guidelines advanced for conducting research during GHEs often take the form of high-level broad principle-like or specific rule-like guidelines. A novel conceptualization of best practice is offered here, as a mid-level translational mechanism, serving as a bridge from *text* to *context*, more specific than principle-like guidelines, yet not so specific as rule-like guidelines. It is helpful to imagine a continuum, upon which abstract and high-level principle-like guidelines exist on one end, and as guidance becomes progressively more detailed, we approach the other end of the continuum,[8] occupied by more prescriptive rule-like guidelines, i.e. solid instruction on what to do. Best practice examples are situated in the middle of this continuum, they are more detailed manifestations of high-level principle-like guidelines and demonstrations of how such guidelines can be applied at a practical level, based on concrete cases, but they lack the prescriptive 'all or nothing' nature of rule-like guidelines.

This conceptualization of best practice combines two important methodologies associated with principle-like guidelines: specification and casuistry. Specification relies on deductive reasoning to progressively narrow the scope of an initial abstract norm and to render it less indeterminate (Richardson, 2000; Beauchamp, 2003). But unlike specification, the movement from the principle-like guidelines towards a practical example of the 'guideline in action' does not tell the decision maker exactly what to do with regards to their own particular situation; rather, it acts as a guide in terms of how the relevant guideline *might be* fleshed-out *through the provision of a real world example*. Most importantly, this serves as a further basis on which to justify the particular decision that is taken in any given context.

It is important to note that the conceptualization of best practice offered here relates to the examples of guidelines in action which are known to work well and which incorporate core values from the principle-like guidelines for which they support interpretation. Although using the terminology of'best' practice, I am not commenting substantively on what constitutes 'best' in a given scenario amongst all possible actions arising from a guideline. If a practice or example has previously been judged as 'best practice', it suggests a degree of (ethical) credential, albeit with the caveat that context is always key. Direct transplants will rarely be possible. Rather best practice instances provide ethical fence posts on the journey towards a concrete and defensible decision.

Seen in this way, best practice then relies upon the ability of the decision maker to draw an analogy between the best practice example offered, and the situation with which they are faced. This is akin to casuistry—case-based reasoning—which implies comparison of a current case or dilemma with an analogous or paradigm case. Such an approach relies on 'the way in which circumstances and maxims appear in the morphology of the case itself and in comparison with similar cases' (Jonsen, 1991: 303). For example, Siedner *et al.* consider

varying approaches taken around emergency measures such as quarantines and closure of public buildings during GHEs. They contrast recent approaches to containment of Ebola—which led to distrust amongst local communities—with previous 'more successful' approaches (earlier Ebola Outbreaks and the Nipah Outbreak) which centred on community partnership. A key lesson learned, is that 'In hindsight, some of the negative fallout from decisions to use extraordinary measures might have been avoided had WHO, in partnership with local community leaders and public health experts, more assertively used their legitimacy to caution against the use of coercive measures without an evidence base' (Siedner *et al.*, 2015: 4). This can represent a paradigm case for drawing analogies should a similar health emergency arise which necessitates quarantine and where cultural practices of local communities and strict international protocol on how to respond to a particular GHE may conflict, where the best practice is 'to promote partnership with local stakeholders and identify locally acceptable response strategies' (Siedner *et al.*, 2015: 1). In contrast with casuistry, best practice has the added advantages of (i) already being 'connected' to the relevant principle-like guidelines, whereas casuistry necessitates that the decision maker first draw analogy (relying upon their own experiences) and then identifies relevant principles and (ii) best practice instantiations are already provided to decision makers, so that they do not have to rely on their own (lack) of experience, but can benefit from the collective experience of the stakeholders involved in identifying best practice instantiations. Furthermore, best practice can help to better incorporate and reflect into guidance the practical realities and experiences of the research community during GHEs.[9] The importance of more grounded decision-making, which addresses important theory practice gaps (Robeyns, 2008) between guidelines and practical issues arising 'on the ground' has been stressed within bioethics for some time (e.g. Wolf, 1994) and more recently so in the context of global health research (e.g. Aellah, Chantler and Geissler, 2016). For example, again in the context of Ebola, the question of the permissibility of using interventions not yet tested on humans was raised (WHO, 2014). Standard international guidance normally advises against such use and a special WHO panel was convened to consider the question, ultimately agreeing that such uses were permissible, subject to certain conditions being met. Should a further GHE arise where similar questions around suitability of untested interventions arise, having readily accessible best practice which reflects these lessons, and the considerations of the convening panel, can provide the research community with the confidence that if they satisfy similar terms and conditions laid out in the case of Ebola, they can make the case for the use of such treatments without time-consuming recourse to a panel.

Consider also the impact of the Zika virus and the question of including pregnant women in clinical trials of vaccines. A recent report from the Ethics Working Group on ZIKV Research and Pregnancy (2017) includes guidance on the inclusion of pregnant women in vaccine development. It is noted that pregnant women have historically been excluded from such research. Drawing upon expertise and lessons learned over the course of the ongoing Zika emergency, the working group offers recommendations on 'the conditions under which is it ethically acceptable, if not required, to include pregnant women in ZIKV vaccine trials' (2017: 1). The authors of the report are clear in laying out the parameters of their guidance, in that it is applicable to 'the current situation of continuing ZIKV outbreaks with limited effective prevention modalities and no existing vaccine approved for use, as well as to any future scenarios in which critical evidence gaps remain on the safety and efficacy of ZIKV vaccines in pregnancy' (2017: 1). It could be argued that the recommendations laid out by the Working Group—particularly regarding their risks/benefits test—could constitute best practice in sufficiently similar scenarios wherein pregnant women are particularly affected by any future GHEs which require the development of new vaccines.

Data sharing represents another useful illustration. Sharing information is becoming increasingly prevalent in the research context. Indeed, in recognition of the significance of the use of data for research purposes, the scope of the recently revised CIOMS Guidelines (CIOMS, 2016) has been extended 'from biomedical research to health-related research because the term biomedical research would not cover research with health-related data'. During GHEs, timely access to accurate data is paramount, particularly to tend to limited evidence bases, identify viruses, understand how they spread and develop effective treatments (e.g. Lurie *et al.*, 2013). There is also a dearth of evidence around effective response mechanisms during GHEs (CIOMS, 2016). Consider the following principle and corresponding best practice instantiation:

Principle: Data controllers should demonstrate their commitment to privacy protection through the development and implementation of appropriate and transparent policies.

Best Practice: Appropriate disclosure control should be applied to all outputs; this should be carried out under the authority and oversight of the designated privacy officer.

Thus, the aforementioned best practice instantiation offers the decision maker one example of how data controllers can balance their commitment to privacy protection with the specific example of disclosure control, but it does not imply that this is the *only* way to demonstrate respect for the initial principle. In addition to (or alternative to) disclosure control, the practical implementation of this principle might include requiring anonymization, pseudonymization or the obtaining of consent. Thus, best practice examples do not necessarily point the decision maker towards a definitive answer. As the Nuffield Council on Bioethics notes, offering an overly specific rule-like norm 'may proscribe solutions that can optimise ethical data use according to legitimate and possibly diverse values' (2015: 87). Rather, by offering practical examples of manifestations of underlying rules and principles, they guide the decision makers towards the 'types' of application which should be made.

It is acknowledged that appeals to best practice will still necessitate the exercise of discretion on the part of the decision maker. Yet, another related advantage of best practice is that where analogies can be drawn between the best practice example included with guidance and the decision being taken in a given situation, decision makers must also justify why they have chosen to rely upon a particular interpretation/draw analogy or equally why they chose not to do so, thus facilitating the important critical reflection and discussion on research governance in the humanitarian setting (e.g. Schopper *et al.*, 2015). One key observation on a recent meeting addressing research and innovation during GHEs (Nuffield Council on Bioethics, 2016: 6) was that:

> Compliance and ethics are different things, and there is no substitute for a moral compass guiding one in what is right to do in an awful situation. At the same time, mechanisms by which people can be held to account for the decisions they make in those situations are needed. . .This is a challenge for regulators and for ethicists: not just guidelines or tick boxes that 'let people off the hook' from using their judgment.

Thus, best practice instantiations can support the necessary and inevitable exercise of discretion on the part of the decision maker, and like principles offer a common language and framework with which to engage in dialogue. However, they avoid the pitfalls of being as vague and as vulnerable to interpretative latitude and disagreement as principles alone. It is acknowledged that the decision maker must still decide when a guideline is applicable, interpret it, balance it against competing guidelines (which must also be interpreted) and draw an analogy with the best practice instantiation provided and the decision which they are facing, and then consider how to implement it in practice. But precise determination is not the telos of the application of best practice instantiations. They are designed to guide decision makers towards the *type* of determination that they should work towards. Such an approach does not, cannot and should not obviate the exercise of discretion. Equally, as has been argued throughout, best practice offers the decision maker more support in exercising this discretion than rules or principles alone.

How Do We Determine What Best Practice Is?

It is appreciated that identification of best practice instantiations is not necessarily a straight-forward task. Indeed, the 'best' in best practice suggests that there is always a morally sound, good outcome, but the adequacy of ideal theory in the disaster setting has been called into question (e.g. Schwartz *et al.*, 2014). It may be that 'best' practice in a given situation is 'the lesser of two evils' or the 'better' action amongst many potential actions, all of which may be nonideal (e.g. O'Mathuna, 2016).

A further challenge is that on its face, 'best practice' can be viewed as a subjective evaluation, and paradigm examples of guidelines in action may vary depending upon whom one asks to provide them. However, certain approaches can contribute towards developing best practice instantiations which genuinely reflect practical, helpful examples from the ground up. This requires collaboration and sharing of experiences amongst key stakeholders—first and foremost—the research community. Such collaborative exercises already take place in the context of guideline development; revision of the updated CIOMS Guidelines involved an iterative and deliberative process which included wide international stakeholder consultation and 'evidence retrieval' based on key literatures and pre-existing guidelines.[10] Similarly, the Ethics Working Group on ZIKV Research and Pregnancy membership comprise clinicians working on Zika and public health as well as bioethicists. The consultation strategy involved engagement with 'experts from a variety of organisations including: global and national public health agencies and regulatory authorities; public and private research institutions; pharmaceutical companies;

public and private funders; medical associations specific to obstetrics and maternal–fetal medicine; and non-profit NGOs working on maternal child health and/or emergency response effort' (2017: 68).

Of paramount importance is the involvement of local communities early on in partnership with the research community (Quinn, 2004; Morin *et al.*, 2008). As Siedner *et al.* (2015: 4) report in considering lessons learned from Ebola:

> A rich institutional knowledge about best practices for community advisory boards exists from the research community and, in combination with recent experience gained through collaborations with community leaders during the current epidemic, can serve as the basis for much-needed guidelines for public health activities. Members should represent divergent interests and include religious leaders, community representatives, non-governmental organizations (NGOs), and other stakeholders. The body should be briefed on the status of the threat and called on to offer recommendations on community desensitization, capacity building, and control measures.

Thus, it is fundamental that best practice is generated *from the ground up*, and that examples offered genuinely reflect the experiences of those involved with conducting and undergoing research-related activities during GHEs and that this is done in a rapid, time-responsive manner.

It is also crucial that examples identified as 'best practice' are constantly kept under review, as circumstantial developments (e.g. discovery of new treatment and exacerbation of spread) may change what constitutes best practice in a given context. Best practice should be monitored and subject to revision, incorporating 'feedback-loops'[11] between researchers who are applying them on the ground and those responsible for disseminating best practice.

Who/WHO Disseminates Best Practice?

Whilst the previous section suggested that a wide variety of stakeholders must be involved in the identification and formulation of best practice, the question of who might be charged with *disseminating* best practice instantiations is also significant. Given their integral role in declaring public health emergencies of international concern and in collaborating with key actors involved in conducting research during such emergencies, it is worthwhile considering whether the WHO might be best placed to act as a 'curator' of best practice instantiations. The WHO could take responsibility for collecting examples offered by numerous actors involved in conducting research during GHEs (e.g. Global Research Collaboration for Infectious Disease Preparedness; Médecins Sans Frontières).

Best practice could then be made readily available on a publicly accessible open repository web platform via the WHO website. Such 'best practice' could ultimately be folded-in to guidance when it is revised, by for example, not only the WHO but CIOMs. This avoids the pitfalls on time lapses associated with reliance on the development of new guidelines. As van Delden and van der Graaf note (2017), the recently revised CIOMS Guidance was anticipated for some time, given the new challenges which had emerged since its previous iteration.

As indicated throughout this article, there is already a pool of best practice instantiations which can be proactively identified in anticipation of future GHEs and already made available to the research community. The WHO also offers best practice in the form of bulletins, such as that on sharing information through data platforms (Moorthy *et al.*, 2016). The WHO Emergency Response Framework (ERF) sets out as one of its core functions to 'promote and monitor the application of national and, where necessary, international, protocols, health standards, methodologies, tools and best practices, continually' (2013: 56).

It is appreciated that such approaches are not without limitations, particularly regarding the challenges of reaching consensus in the development of best practice (Schuklenk, 2017), as each individual or organization consulted will inevitably reflect their own version of best practice which is informed by their experiences and bias. Furthermore, like any regulatory mechanism, best practice can only take us so far in terms of addressing the many complexities involved in research during GHEs. For example, the exclusion of pregnant women in research speaks to wider issues such as the classification of pregnant women as a 'vulnerable population' (van der Zande *et al.*, 2017). Best practice may represent one potential mechanism of demonstrating more 'proactive and intentional inclusion of pregnant women's interests in the R&D agenda' (Krubiner and Faden, 2017) but one which is reliant upon wider change, including more facilitative overarching guidelines. Thus, the suitability of best practice instantiations is dependent upon the appropriateness of higher-level guidelines, the interpretation of which best practice are designed support; if the first-order principles or rules are ethically problematic, they may give rise to problematic best practice. Just as best practice must be constantly kept under review, reflective equilibrium (Rawls, 1971) of overarching principles and rules is fundamental.

It must also be noted that whilst the inclusion of best practice is imperative, it is but one element of the complex landscape of GHEs and research. Wider factors are also in play, including power-relations, socio-cultural and historical factors, and these dynamics may persist regardless of the decision-making approach adopted. Further consideration of such factors is beyond the scope of this article, but these limitations should not denigrate from the significance of ensuring that the best procedures are in place to identify, collate and share best practice, which should be an inclusive process which genuinely engages with key stakeholders and the variety of issues which must be considered when conducting research during GHEs, particularly around engagement with communities.[12]

Where No Current Best Practice Exists

A final challenge to the introduction of best practice in guidance is where no current best practice exists. This will be particularly relevant when considering the governance of novel technologies or research methodologies in the wake of previously unexperienced GHEs. As with legislation in general, the challenge of being unable to foresee every possible eventuality remains. It is argued that best practice remains invaluable nonetheless in a wide-array of settings where pre-established best practice does exist, but where it has not yet been captured alongside guidelines. Further, there is an important role to be played by third party actors in supporting researchers (Laurie *et al.*, 2018), which, it is argued here, also includes a responsibility to identify possible instances of best practice across a range of settings, even perhaps where connections across different contexts may not be immediately apparent. Indeed, the GHE context gives rise to numerous opportunities for sharing best practice as cooperation between different actors becomes more prolific, particularly by virtue of the number of collaborative frameworks and networks which appear to be increasing. Further research into the ways in which best practice instantiations are identified, developed, proliferated, used and revised is also needed to make the most out of these decision-making aids.

Conclusion

This article has offered insights into a previously overlooked yet integral aspect of conducting research during GHEs, i.e. analysis of the suitability of principle-like and rule-like guidelines. Further, it has demonstrated the necessity and value of including best practice instantiations alongside pre-existing guidelines. It has been argued that current principle-like and rule-like guidelines are inadequate on their own; they still leave the decision maker in need of additional support to determine what to do. Best practice instantiations represent an important interpretative tool which tends to this gap. They offer the decision maker examples of the ways in which guidelines ought to be interpreted, whilst retaining necessary flexibility to tailor norms appropriately according to the specific demands of the decision at hand. Furthermore, best practice also provides a means of capturing lessons learned from previous GHEs and incorporating them into future decision-making. A key lesson which emerges time and time again in the aftermath of GHEs is our need to be better prepared for the next GHE, providing the research community with pre-existing best practice instantiations can better arm the community with decision-making support for when the next emergency hits, rather than the current tendency to learn after an event. Just as 'we have to break from the habit of funding from crisis to crisis' (Stinchcomb, 2016), we must also break the habit of failing to learn from the past. Indeed, the inclusion of best practice alongside guidelines ensures that our past experiences render us better prepared for the future.

Notes

1. GHEs are interpreted in this article to include not only WHO declared PHEICs, but additionally, 'disasters' and 'humanitarian crises' that may fall out with the WHO definition, but which nonetheless carry with them the same implications as PHEICs. Note that for the purposes of this article, I refer to GHE throughout and only use the term PHEIC when making specific reference to PHEICs declared as such by the WHO.
2. For broader discussion, see Ganguli Mitra and Sethi (2016) Conducting research in the context of GHEs: identifying key ethical and governance issues. Nuffield Council of Bioethics Background Paper, available at: http://nuffieldbioethics.org/wp-content/uploads/Research-in-global-health-emergencies-background-paper.pdf.
3. See for example: Laurie (2017) and Lyall *et al.* (2009).

4. For discussion see Musschenga (2005); Aveling *et al.* (2016).
5. See, for example Bix (1998); Harris (2003); Greer (2004) and Albertzart (2014).
6. See for example, the work of Innovative Support to Emergencies Diseases and Disasters (InSTEDD), available from: http://instedd.org/ [accessed 10 July 2017] and Coyle and Meier (2009).
7. Testimony of Edward Cox, director, Office of Microbial Products, U.S. Food and Drug Administration. Public Webinar with International Regulators of the Committee on Clinical Trials during the 2014–2015 Ebola Outbreak. WebEx, May 2016 as cited in Cohen and Kupferschmidt (2014: 47).
8. Goodin has suggested that rules are more detailed principles, and that the relationship between them can be described as existing upon a continuum: see Goodin (1982).
9. See for example, Nuffield Council on Bioethics workshop (2016).
10. For a detailed account of the revision process, see: Van Delden (2016).
11. On feedback loops, see Taylor-Alexander *et al.* (2016) and Ganguli-Mitra *et al.* (2017).
12. See for example, the work of MESH, particularly in identifying 'good practices', available from: https://mesh.tghn.org/ [accessed 14 July 2017].

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